

Alcohol and Women: An Overview

Inborn differences shape each individual's response to alcohol, including the risk of developing complications from alcohol abuse. Some of these inborn differences may be related to gender: women seem to be more vulnerable than men to alcohol-related liver disease, cardiovascular disease, and brain damage.

The reasons for this vulnerability are not well understood. Women, on the average, are less likely than men to consume alcoholic beverages or to drink heavily or even moderately (Dawson and Archer 1992). Among women who do consume alcohol, their drinking patterns tend to be quite different from those of men. Men's drinking often is characterized by infrequent "binge" episodes, whereas women tend to drink more frequently but ingest smaller amounts of alcohol on each occasion (Dawson 1996). As the studies described below illustrate, however, women develop alcohol-related complications after drinking smaller cumulative amounts of alcohol than men do.

Health Consequences of Alcohol for Women

Women develop alcoholic hepatitis and alcoholic cirrhosis after the ingestion of smaller daily amounts of alcohol than men do (Mezey et al. 1988a). A recent large prospective study followed 13,000 adults for 12 years to determine the association between self-reported alcohol intake and the risk of future liver disease (Becker et al. 1996). The study found that the level of drinking above which there was a risk of alcohol-induced liver disease and alcoholic cirrhosis was 7 to 13 drinks (84 to 156 grams of alcohol) per week for women but 14 to 27 drinks (168 to 324 grams of alcohol) per week for men. Intake of 28 to 41 drinks (336 to 492 grams of alcohol) per week increased the risk of developing cirrhosis of the liver during the 12-year period 17 times for women and 7 times for men (compared with the minimal risk experienced by women or men

drinking one to six drinks per week). Women, in addition, were found to be at higher risk of developing liver disease at any given level of alcohol intake.

Alcoholic women are more susceptible than alcoholic men to the development of myopathy (degenerative disease of skeletal muscle) and cardiomyopathy (degenerative disease of heart muscle). In a study of alcoholic women and men who had no symptoms of muscle disease, myopathy—indicated by clinical muscle weakness and evidence on microscopic examination of biopsy tissue—and cardiomyopathy were present in half of the women. These conditions were at least as common in women as in men, although the lifetime alcohol consumption for alcoholic women was only 60 percent that of alcoholic men (Urbano-Marquez et al. 1995). For both women and men, the severity of the deficiencies in muscle function was correlated to the total lifetime dose of alcohol, but the threshold dose for women for the development of cardiomyopathy was much lower. In alcoholics with a diagnosis of alcoholic cardiomyopathy, the women reported a lower daily dose of alcohol, shorter duration of alcoholism, and lower lifetime consumption (Fernandez-Sola et al. 1997).

Alcoholic women perform worse on neuropsychological tests of immediate recall and psychomotor speed than do alcoholic men with similar drinking histories (Acker 1986). Computer tomography scans showed decreases in brain volume in alcoholic women after a shorter length of excessive drinking compared with alcoholic men (Mann et al. 1992). In a more recent study using magnetic resonance imaging scans, the area of the corpus callosum (the primary nerve fiber bundle connecting the two cerebral hemispheres) was smaller in hospitalized alcoholic women than either control women or hospitalized alcoholic men (Hommer et al. 1996). In this study, alcoholic women and men had similar lifetime alcohol consumption. This study suggests an

increased sensitivity to alcohol-induced brain damage among women who drink. Although alcohol-induced decreases in brain volume are sometimes reversible following sobriety (Carlen and Winkinson 1987), the effect of long-term sobriety on the reduced corpus callosum size in alcoholics is unknown.

Finally, mortality rates are higher among women than men who drink heavily. The most frequent causes of mortality among alcoholic women are alcoholic liver disease, pancreatitis, accidents or violence, suicide, cancer, and cardiovascular disease (Lindberg and Ågren 1988; Smith et al. 1983). Heavy alcohol ingestion places young women (up to 55 years old) at increased risk of death from cardiovascular disease. In a study that compared causes of death among drinkers versus abstainers, 11.2 percent of women who consumed more than two alcoholic drinks per day died of cardiovascular disease, compared with 3.5 percent of women who abstained. For men in the same age group, 11.6 percent of those who consumed at least two alcoholic drinks per day died of cardiovascular disease, versus 8.4 percent of nondrinkers (Hanna et al. 1992).

Physiologic Mechanisms

Current research provides hints, but not by any means a complete picture, of the differences in the metabolism of alcohol between women and men, and at a finer level, hormonal and cellular differences that may lie behind differences in health consequences.

As a first step in determining why women seem particularly vulnerable to alcohol-induced damage, scientists have investigated whether there are differences between women and men in the way alcohol is absorbed into the bloodstream and metabolized. Making such comparisons is difficult. Physical characteristics such as body size and weight can influence the processing of alcohol, and genetically determined factors result in sizable differences in alcohol metabolism rates among individuals. Individuals' drinking history and how they consume alcohol—moderate amounts over time or binges, and in the context of what health history and age—can affect alcohol

metabolism. Finally, differences in how the effects of alcohol are studied—how it is administered, over what time course, with or without food, and at what time of day—also can influence the resulting observations (Thomasson 1995).

One uniformly observed difference between women and men is that women attain higher peak blood alcohol levels than men when ingesting the same dose per kilogram of body weight. The higher peak blood levels are principally related to the distribution of alcohol—a water-soluble substance—in the smaller body water content of women compared with men (Jones and Jones 1976; Marshall et al. 1983).

Accounting for the difference in body water content is one of the difficulties in documenting the presence of other gender-related differences in alcohol metabolism and to what extent they contribute to the higher postconsumption blood alcohol level in women, and ultimately, alcohol-related health consequences. In particular, the extent to which there are differences between women and men in alcohol metabolism in the stomach—before alcohol reaches the liver, which is the primary site of alcohol processing—remains unclear (Thomasson 1995).

Studies also have differed on whether alcohol elimination rates—a reflection of how quickly the enzyme alcohol dehydrogenase (ADH) in the liver processes alcohol—are different in women and men (Arthur et al. 1984; Marshall et al. 1983; Mishra et al. 1989; Thomasson 1995). One approach to investigating this issue is examining whether sex hormones can influence elimination rates. No consistent changes in rates of alcohol elimination have been found during the various phases of the menstrual cycle (Gil 1997). However, higher levels of acetaldehyde—a toxic by-product of alcohol metabolism—were evident after alcohol ingestion in women during high estradiol phases of the menstrual cycle or in women taking oral contraceptives (Ericksson et al. 1996). Removing the ovaries of female rats has no influence on liver ADH or on rates of alcohol elimination (Mezey et al. 1981). Removal of the testes in humans with metastatic prostate cancer,

however, decreased plasma testosterone levels and increased rates of alcohol elimination (Mezey et al. 1988*b*), and, in another study, administration of dihydrotestosterone each day for 14 days decreased alcohol elimination in healthy men (Varbourdolle et al. 1991), suggesting that testosterone may have a measurable influence on alcohol elimination rates.

Finally, recent studies indicate that women have larger liver volumes per unit body weight than men do, which could result in higher rates of alcohol elimination when expressed per kilogram of body weight in women than in men (Kwo et al. 1997). The implication is that a larger liver will have more ADH available to metabolize alcohol. Additional research is needed to clarify the relative alcohol metabolic rates in women and men and the mechanisms behind gender-related differences.

Liver Injury

Similarly, the mechanism for the increased susceptibility of women to alcoholic liver disease is uncertain. One possibility is that higher relative rates of alcohol elimination in women than in men—a difference that has been noted in rodent studies but remains to be confirmed in humans—would result in more rapid formation of toxic metabolites such as acetaldehyde. Acetaldehyde is a very reactive compound that has been implicated in liver injury by stimulating the formation of free oxygen radicals, by-products of metabolism that can cause tissue damage.

Some research suggests that there may be gender-related differences at the cellular level that make women more susceptible to alcohol-related liver disease. One of the important contributors to alcoholic liver injury is activation of Kupffer cells, a type of immune cell that is resident in the liver, by alcohol. This activation is enhanced further in the presence of endotoxin, a component of the cell walls of bacteria found in the gut. The Kupffer cells are then stimulated to produce chemical mediators of the inflammatory process that can have either protective or destructive effects (see the section “Alcohol-Induced Liver

Injury” earlier in this chapter). One group of investigators reported that Kupffer cells of acutely intoxicated female rats produced higher levels of tumor necrosis factor alpha (TNF- α or TNF, one of the proinflammatory mediators) than did Kupffer cells of intoxicated male rats (Spitzer and Zhang 1996). The actual amounts of TNF appeared to vary according to the phase of the estrus cycle. Interestingly, the females exhibited an attenuated, and thus less destructive, response to endotoxin by neutrophils, another immune cell. This may be a compensatory protective mechanism to reduce the potential for tissue injury by TNF. Finally, a recent finding suggests the involvement of estrogen in the greater sensitivity of female alcoholics to liver injury. Serum TNF levels and TNF messenger ribonucleic acid in the liver of female rats after endotoxin treatment were twice as high if the animals were pretreated with estrogen (Ikejima et al. 1998).

Many of the advances in our understanding of liver disease have resulted from the development of a clinically relevant animal model where continuous intragastric (directly to the stomach) feeding over a period of weeks mimics the progression of liver injury (the so-called French-Tsukamoto model) (French et al. 1986; Tsukamoto et al. 1985). This model recently was tested in female rats (Iimuro et al. 1997). Male and female rats were continuously given alcohol equivalent to 28 to 35 percent of total calories in a liquid high-fat diet for up to 4 weeks. Even though blood alcohol concentrations and rates of alcohol elimination were the same for the two genders under these conditions, female rats developed steatosis (abnormal fat deposition in the liver), inflammation, and necrosis (tissue death) more rapidly and to a greater extent than the males did, a picture that mimics the clinical situation. Other indicators of liver injury, including elevated plasma endotoxin levels, also were higher for females. The use of this model will facilitate investigations into the underlying mechanisms for greater female sensitivity to alcohol-induced liver injury and possibly other forms of tissue injury.

In Closing

As with liver disease, the mechanisms for the differential impact of alcohol on heart disease and mortality and on neurologic function in women and men are still unclear. There remain possibilities at every level of alcohol processing—its metabolism by enzymes in the stomach and liver, its absorption into the bloodstream, and its actions on the physiology of end organs—for mechanisms that could contribute to gender-related differences in the health consequences of drinking. The fact that adverse effects have been observed at levels of consumption that many would regard as low—7 to 13 drinks per week (Becker et al. 1996)—bespeaks the importance of research aimed specifically at identifying why women are so vulnerable to alcohol. The next two sections in this chapter discuss the impact of alcohol on two diseases—osteoporosis and breast cancer—that predominantly affect women.

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